REMARKS

Claims 32-43 are pending. Claims 19-22 and 26-27 have been cancelled without prejudice or disclaimer as being drawn to non-elected inventions. Claims 1-18, 23-25 and 28-31 were canceled and claims 32-43 were added. The specification was amended to provide a more descriptive title, to correct typographical errors, to include SEQ ID NOs, and to replace the pending sequence listing with the enclosed sequence listing in compliance with 37 C.F.R. §§1.821-825. Support for new claim 32 can be found in, *e.g.*, page 19, line 28 to page 20, line 6, Table 1, and originally filed claim 9. Support for new claims 33 and 39 can be found in, *e.g.*, page 7, lines 27-30. Support for new claims 34 and 40 can be found in, *e.g.*, page 32, lines 11-14. Support for new claims 35 and 41 can be found in, *e.g.*, page 23, line 13 to page 24, line 7. Support for new claims 36 and 42 can be found in, *e.g.*, originally filed claim 5. Support for new claims 37 and 43 can be found in, *e.g.*, page 23, lines 17-23. Support for new claim 38 can be found in, *e.g.*, page 19, line 28 to page 20, line 6; Table 1; and originally filed claim 3. No new matter has been added by these amendments.

The Specification.

The Examiner has indicated that the title is not descriptive. In response, Applicants note that the title has been amended herein to recite "INTERFERON-BETA-1a - IMMUNOGLOBULIN FUSION PROTEINS AND USES." Applicants assert that the title as amended is clearly indicative of the invention to which the pending claims are directed.

The Drawings.

The Examiner has indicated that the legend for Figure 2 is not descriptive, and points to a typographical error in the numbering of the DNA sequence. Applicants thank the Examiner, and note that the legend for Figure 2 has been amended to number Figure 2 as Figure 2A-1, 2A-2 and 2B, and to correctly indicate the numbering of the DNA sequence.

Claim objections.

The Examiner has objected to claim 6 for having two periods. Claim 6 has been cancelled. This objection is therefore moot and can be withdrawn.

Rejection Under 35 USC § 112, first paragraph

Written Description.

Claims 1, 3, 6-10, 12, 15-18, and 28-31 are rejected for lack of written description. The Examiner states that "[o]ther than the mutants described on page 35, the specification does not disclose all the mutants or portions thereof the polypeptide." (See Office Action, paragraph bridging pages 3-4). The Examiner further states that "[t]he specification does not provide written description for the following term: mutant and portions of the polypeptide." (See Office Action, page 4). Claims 1, 3, 6-10, 12, 15-18, and 28-31 have been canceled. Applicants traverse this rejection to the extent it applies to new claims 32-43.

New independent claims 32 and 38 recite specific SEQ ID NOs. New claim 32 recites SEQ ID NO: 60, corresponding to the wild-type interferon-beta-1a polypeptide, disclosed in, *e.g.*, Table 1. New claim 38 recites SEQ ID NOs: 45-59, corresponding to the interferon-beta mutants disclosed in, *e.g.*, Table 1 and Example 1. Claims 33-37 and 39-43 depend, either directly or indirectly, from either claim 32 or claim 38, and therefore incorporate all the limitations of these independent claims. It is therefore clear that Applicants were in possession of the invention claimed in new claims 32-43. Thus, this rejection should be withdrawn.

Enablement.

Claims 1, 3, 6-10, 12, 15-18, and 28-31 are rejected for lack of enablement. The Examiner states that "the specification, while being enabling for mutant human IFN-β described on page 35 does not reasonably provide enablement for other mutant human IFN-β's or portion of the polypeptide." (See Office Action, page 4). Claims 1, 3, 6-10, 12, 15-18, and 28-31 have been canceled. Applicants traverse this rejection to the extent it applies to new claims 32-43.

As stated *supra*, new claims 32 and 38 recite specific SEQ ID NOs corresponding to the wild-type interferon-beta-1a polypeptide or the fifteen interferon-beta mutants disclosed in, *e.g.*, Table 1, and Example 1. Each of these mutants has one or more activities described in, *e.g.*, pages 44-45 and Figures 3-7.

The wild-type interferon-beta-1a polypeptide and the fifteen claimed interferon-beta-1a mutants are fully disclosed at, *e.g.*, Table 1 and Example 1. Therefore, Applicants assert that new claims 32-43 are fully enabled by the specification as filed. Thus, this rejection should be withdrawn.

Rejection Under 35 USC § 112, second paragraph

Claims 1, 3, 6-10, 12, 15-18 and 28-31 are rejected for indefiniteness. Claims 1, 3, 6-10, 12, 15-18 and 28-31 were canceled. Applicants traverse this rejection to the extent it applies to new claims 32-43.

The Examiner states that claims 1, 6-10 and 15-18 are indefinite for reciting the term "portion thereof." (See Office Action, page 7). Claim 1 has been canceled and new claims 32-43 do not recite the phrase "portion thereof."

The Examiner also states that claims 3, 12 and 28-31 are vague and indefinite for reciting the term "mutant." (See Office Action, page 8). Claims 3, 12 and 28-31 have been canceled herein. New claim 38 specifically recites the amino acid sequences of SEQ ID NOs 45-59, which correspond to the fifteen interferon-beta mutants disclosed in, *e.g.*, Table 1, and Example 1.

The Examiner further states that claims 29 and 31 are indefinite for depending upon method claim 27. Applicants note that claims 29 and 31 have been canceled herein. For these reasons, these rejections should be withdrawn.

Rejection Under 35 USC § 103(a)

Claims 1-18, 23-25 and 28-31 are rejected as being obvious over Chang et al. (US Patent 5,908,626) ("Chang") and Bell et al. (US Patent 4,914,033) ("Bell") in view of Capon et al. (US Patent 5,116,964) ("Capon") and Katre et al. (US Patent 4,766,106) ("Katre"). According to the

Examiner, Chang discloses a hybrid recombinant protein consisting of human interferon-β and a human immunoglobulin Fc fragment, and Bell teaches the mutation of interferon-β in order to increase antiviral activity. (See Office Action, page 9). According to the Examiner, Capon discloses the generation of fusion proteins with at least functionally active hinge, CH2 and CH3 domains of the constant region of an immunoglobulin, and Katre teaches the conjugation of interferon-β to polymers. (See Office Action, pages 9-10). Claims 1-18, 23-25 and 28-31 were canceled. Applicants traverse this rejection to the extent it applies to new claims 32-43. New claim 32 requires a polypeptide comprising the amino acid sequence of SEQ ID NO:60 (corresponding to the wild-type amino acid sequence of the interferon-beta-1a polypeptide) and a hinge, a CH2 and a CH3 domain of an immunoglobulin. New claim 38 requires SEQ ID NOs: 45-59 (corresponding to the interferon-beta mutants disclosed in, *e.g.*, Table 1 and Example 1) and a hinge, a CH2 and a CH3 domain of an immunoglobulin. Claims 33-37 and 39-43 depend, either directly or indirectly, from either claim 32 or claim 38, and therefore incorporate all the limitations of these independent claims.

The Examiner admits that Chang does not teach the constant region of the immunoglobulin comprising at least a hinge, a CH2 and a CH3 domain. Also, Chang does not disclose the specific interferon-beta-1a amino acid sequences as required by the pending claims. Further, Chang requires a peptide linker not recited in the pending claims, and Chang teaches away from hybrid recombinant proteins lacking a peptide linker at col. 1, lines 51-55, stating "such hybrids can present problems in that the peptide at the C-terminal of the active moiety and the peptide at the N-terminal of the Fc portion at the fusion point creates a new peptide sequence, which is a neoantigen, and which can be immunogenic."

Bell, Capon and Katre do not cure this deficiency. Bell, while disclosing interferon-beta-1b and mutants thereof, does not disclose the specific interferon-beta-1a or mutant amino acid sequences as required by the pending claims. Nor does Bell teach the addition of a constant region of the immunoglobulin comprising at least a hinge, a CH2 and a CH3 domain. Similarly, Capon does not teach or suggest the use of any interferon polypeptide, much less the specific amino acid sequences of the pending claims. Finally, Katre only discloses interferon-beta-1b. As discussed above, new claims 32-43 recite specific interferon-beta-1a or mutant amino acid sequences not taught or suggested by Katre. As such, the cited references do not render obvious

the claims as amended herein, and this rejection can be withdrawn.

CONCLUSION

Applicants submit that the application is in condition for allowance and such action is respectfully requested.

Should any questions or issues arise concerning the application, the Examiner is encouraged to contact Applicant's undersigned attorney at the telephone number indicated below.

Respectfully submitted,

March 24, 2003

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the title:

The title was amended as follows:

-- INTERFERON-BETA-1a - IMMUNOGLOBULIN FUSION PROTEINS AND USES --

In the specification:

The paragraph beginning on page 4, line 28 was amended as follows:

-- Figure 2. **cDNA and deduced amino acid sequence for an interferon-beta- la/Fc fusion.** The full DNA and protein sequences of the human EFN-beta- la/mouse Fc are shown in Figures 2A-1, 2A-2 and 2B. The human EFN-beta- 1 a protein sequences span amino acid residues 1- 166 (DNA sequences 1-498). The enterokinase linker sequence spans amino acid residues 167-171 (DNA sequences 499-513). The murine IgG2a heavy chain protein sequence spans residues 172-399 (DNA sequences 514-1197[437]). --

The paragraph beginning on page 23, line 24 was amended as follows:

-- Other derivatives of interferon beta/ Ig include covalent or aggregative conjugates of interferon beta or its fragments with other proteins or polypeptides, such as by synthesis in recombinant culture as additional N-termini, or C-termini. For example, the conjugated peptide may be a signal (or leader) polypeptide sequence at the N-terminal region of the protein which co-translationally or post-translationally directs transfer of the protein from its site of synthesis to its site of function inside or outside of the cell membrane or wall (e.g., the yeast alpha -factor leader). Interferon beta receptor proteins can comprise peptides added to facilitate purification or

identification of interferon beta (e.g., histidine/interferon-beta-la fusions). The amino acid sequence of interferon beta can also be linked to the peptide Asp-Tyr-Lys-Asp-Asp-Asp-Asp-Lys (DYKDDDDK; SEQ ID NO: 61) (Hopp et al., Bio/Technology 6:1204,1988.) The latter sequence is highly antigenic and provides an epitope reversibly bound by a specific monoclonal antibody, enabling rapid assay and facile purification of expressed recombinant protein. This sequence is also specifically cleaved by bovine mucosal enterokinase at the residue immediately following the Asp-Lys pairing.--

The paragraph beginning on page 34, line 5 was amended as follows:

-- The full set of alanine substitution mutations are depicted in Table 1(next page). The names of the mutants specify the structural regions (helices (A (A1 (SEQ ID NO:45), A2 (SEQ ID NO:46)), B (B1 (SEQ ID NO:50), B2 (SEQ ID NO:51), C (C1 (SEQ ID NO:52), C2 (SEQ ID NO:53)), D (SEQ ID NO:56), E (SEQ ID NO:59)) and loops (AB1 (SEQ ID NO:47), AB2 (SEQ ID NO:48), AB3 (SEQ ID NO:49), CD1 (SEQ ID NO:54), CD2 (SEQ ID NO:55), DE1 (SEQ ID NO:57), DE2 (SEQ ID NO:58))) in which the mutations were introduced. The entire panel of alanine (serine) substitutions results in mutation of 65 of the 166 amino acids of human IFN-beta (SEQ ID NO: 60).--